



Maternal Obesity and Neural Tube Defects - A Malaysian Perspective (Interim Analysis)

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Authors' contributions

This work was carried out in collaboration among all authors. Author VJTA conceptualized and developed the proposal, implemented and supervised the research. Author NAD supervised, proof-read and assisted with data analysis. Author TLJ contributed to the data collection, analysis of data and to the writing of the manuscript. Authors SP and RM managed the literature review and data collection. Author RJ assisted with implementation of the research project.

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ABSTRACT

Aim: To determine the incidence of maternal obesity and maternal characteristics of Malaysian women with neural tube defects (NTD)-affected pregnancy.

Methods: This was a single-center retrospective analysis involving women with NTD-affected pregnancy in Sultanah Aminah Hospital from the Johor Bharu region of Malaysia in year 2015. Subjects' body mass index (BMI; kg/m²) during their first antenatal visit was obtained and categorized into six groups: underweight (<18.50), normal weight (18.50-24.99), overweight (25-29.99), obesity Class I (30-34.99), obesity Class II (35-39.99) or obesity Class III(≥40). Data on maternal characteristics including age, ethnicity, gravidity, period of amenorrhea (POA) at booking and diabetic status was also collected.

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Results: There were a total of 17 subjects with NTD-related pregnancy, providing an incidence of 1.2 per 1000 deliveries. The most common NTD diagnosis was anencephaly (n=9;52.9%). Mean age of the subjects was 30±4.7 years. The majority of subjects were Malay ethnicity (58.5%), multigravida (70.6%), has a booking of less than 20 weeks of POA (82.4%) and non-diabetics (52.9%). Mean and standard deviation of the subject's BMI was 25.45±5.07 kg/m². The distribution of under-to-normal weight (BMI < 25), overweight and obese classification were 53%, 29.4% and 17.6% respectively.

Conclusion: The incidence of maternal obesity in women with NTD-affected pregnancy was 17.6% from the study population. Almost half of the subjects were under- and normal weight.

As this is an interim analysis, a bigger sample is required to provide a deeper understanding on the effect of maternal obesity and NTDs.

Keywords: Maternal obesity; neural tube defects; congenital anomaly; pregnancy.

ABBREVIATIONS

BMI : Body Mass Index
CI : Confidence Interval
HSAJB : Hospital Sultanah Aminah, Johor Bharu
NICU : Neonatal Intensive Care Unit
NOR : National Obstetrics Registry
NTD : Neural Tube Defects
POA : Period of Amenorrhea
TOP : Termination of Pregnancy

1. INTRODUCTION

Congenital anomalies, commonly referred to as birth defects, congenital malformations or congenital abnormalities, are defined as anomalies that happen in-utero that may be structural or functional and can be detected prenatally, at birth, or later in infancy [1]. Despite global effort in fortification of folate in food products, NTDs remain the commonest type of major congenital malformation worldwide [2]. Globally, an estimation of 260,100 NTD-affected birth (including livebirths, stillbirths and elective termination of pregnancy) occurred in 2015, giving the worldwide prevalence of NTD-affected livebirth as 18.6 per 10,000 livebirths [3].

There are various theories that explain the etiology of NTDs, which generally stems from a multifactorial cause. The well-known risk factor that cause increased risk of NTDs is folic acid deficiency, which has led to the worldwide effort in folate food fortification. The protective effect of folic acid fortification can be seen in a global-based research, which showed a significantly higher prevalence of NTDs in world region that has not mandate legislation of folic acid fortification in food [4]. One of the recently proposed etiology of NTDs is maternal obesity. This association could be explained by the body

distribution of folic acid in women with obesity. A study has showed obesity could influence folate pharmacokinetics in women of childbearing age by reducing serum folate concentration, which could be explained by increased body adiposity or volumetric dilution of the blood [5].

In 2018, the meta-analysis by Huang, Chen and Feng [6] published supports maternal obesity as a significant risk factor for the development of NTDs. From the analysis of 22 studies, consisting of 1,758,832 women, the findings showed a summary OR of 1.632 (95% CI 1.473-1.808) when compared with pregnant women who are normal weight and overweight, and 1.682 (95% CI 1.510-1.873) when compared with normal weight pregnant women. Furthermore, a dose-response analysis of the 22 included studies had demonstrated a positive relationship between maternal body mass index (BMI) and NTDs: for every 1 kg/m² increase in maternal BMI, the odds of having NTDs in their offspring are higher by 1.027% (OR=1.027; 95% CI 1.004 – 1.051) [6]. Most of the included studies originated from the United States, there were two studies each from China and Sweden respectively, and Iran and Austrian each contributed one article.

Similarly in 2008, Rasmussen and co-researchers [7] published a meta-analysis on NTD and maternal obesity. From their analysis, the risk of NTD is 1.7-fold higher in maternal obesity and more than 3-fold higher in women who are severely obese. The results indicate an odds ratio (OR) of 1.22 [95% Confidence Interval (CI) 0.99-1.49], 1.70 (95% CI 1.34-2.15) and 3.11 (95% CI 1.75-5.46) for overweight, obese and severely obese women respectively, to have pregnancy affected by NTDs as compared with women with normal body weight. All but two of the included studies originated from the United

States and none were from the Asian region. International literature has been able to demonstrate an association between increased maternal BMI and risk of developing NTDs in the offspring, however research to support this theory is scarce in the Asian region.

A search of literature revealed not many studies have been conducted to study this association in the Asian region. Recently, a large population-based cohort study in China had noted a significant increased risk of spina bifida among pregnant women who were obese [8]. An earlier study in China provided similar results as they showed a significant rise in risk of NTDs in obese women after adjusting for confounders such as age, occupation, level of education, family income, parity and folic acid supplementation [9].

In Malaysia, there were several published studies with topics relevant to NTDs [10-12]. However, these studies did not highlight the maternal characteristics of women with NTD-affected pregnancies, as their study primarily focused on neonatal characteristics. This indicates there is still a lack of understanding on maternal characteristics, in particular maternal obesity, in women with NTD-affected pregnancy. Therefore, with the lack of information available in Malaysia on this issue, our study aims to determine the incidence of maternal obesity and maternal characteristics in NTD-affected pregnancy. The hypothesis of this study is that there will be more women who are overweight and obese in the study population, compared to women of normal healthy BMI.

2. MATERIALS AND METHODS

2.1 Study Design

A retrospective analysis of data was performed from January 2019 to June 2019. The study population included women who was admitted due to NTD-affected pregnancies (including livebirths, stillbirths and terminations of pregnancy) between 1st January 2015 to 31st December 2015 to the Sultanah Aminah Hospital from the Johor region of Malaysia.

2.2 Main Variables

The main variable of this study is maternal Body Mass Index (BMI) at booking visits. Booking is defined as the first antenatal encounter to health professionals. BMI was computed from measured weight in kilograms (kg) and height in meters (m) using the formula kg/m^2 . We

categorized the BMI of women based on the international classification from World Health Organization into six groups: [13] underweight (BMI < 18.5), normal weight (BMI 18.5 to < 25), overweight (BMI 25 to < 30), obesity Class I (30 to < 35), obesity Class II (35 to < 40) or obesity Class III ($= >40$). The Royal College of Obstetrics and Gynaecology has also defined pregnant women with obesity as having a BMI of 30 kg/m^2 or greater [14]. Data was excluded if there are missing data on the patient's height and/or weight.

We measured the presence of any types of NTD as the main outcome of the study. The confirmation of NTD was obtained via the medical record of the women. Data was excluded if it was a non-NTD diagnosis, ambiguous or uncertain diagnosis.

2.3 Covariates

Information regarding age, ethnicity, parity, period of amenorrhoea (POA) at booking and diabetic status of the patients were obtained from their respective medical records. Maternal age was calculated from the women's date of birth. The ethnicity is the ethnicity recorded from the medical records. Parity was categorized as primigravida or multigravida. POA at booking was recorded in number of weeks and days. Diabetic status was defined as non-diabetic, pre-existing diabetes or gestational diabetes based on their medical history and oral glucose tolerance test results.

2.4 Data Sources

To ensure all NTD-affected pregnancies was included in this study, data was extracted according to three entities: livebirth, stillbirth and terminated pregnancy. The data were sourced from the neonatal intensive care unit (NICU), labor room and gynecology ward records. As the existing ward records had categorized NTD-affected patients into the heading of 'congenital anomaly', data on the diagnosis had to be extracted from the paper-based medical records of the patients. Confirmation of NTD diagnosis was obtained from the paper-based medical records of these patients. For the purpose of data comparison between cases and the general obstetric population, the summary data of all deliveries (including livebirth and stillbirth) in the Sultanah Aminah Hospital for year 2015 was obtained from the National Obstetrics Registry (NOR). The process of data extraction is shown in Fig. 1.

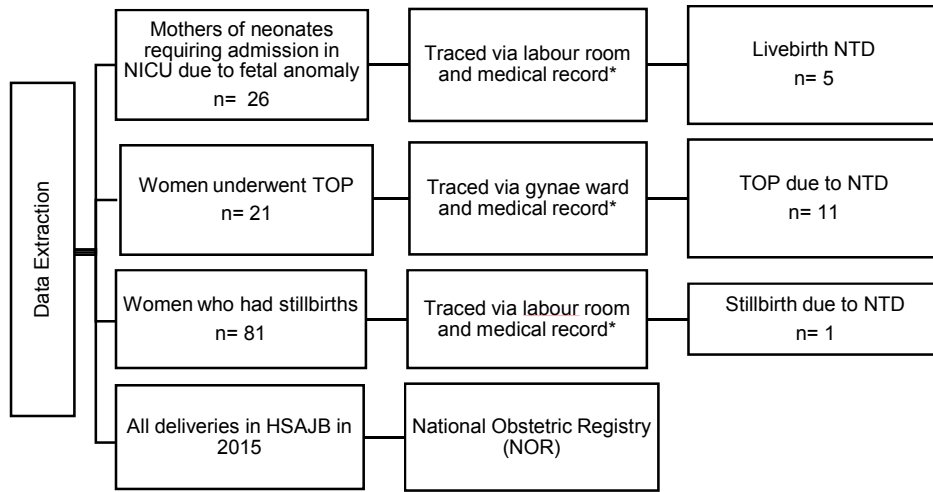


Fig. 1. Overview of the process of data extraction. NTD-affected livebirth was initially identified from NICU admissions due to fetal anomaly and traced back to the record of the mother from the labour room records. Terminated pregnancies related to NTDs were identified from the gynaecology ward records. NTD-affected stillbirth was identified from the labour room records. These ward records have categorised NTD into the heading of ‘congenital anomaly’.

Subsequently, the paper-based medical records of these patients were obtained to ascertain the diagnosis of NTDs. Subjects with confirmed written NTD diagnosis was included in this study. Additional data regarding all deliveries in HSAJB in 2015 from NOR was also obtained

**Patients with non-NTD diagnosis, no admission records and patients with unlocated medical records were excluded. (NTD – neural tube defect; NICU – neonatal intensive care unit; NOR – National Obstetric Registry; HSAJB – Hospital Sultanah Aminah, Johor Bharu; TOP – Termination of pregnancy)*

2.5 Statistical Analysis

Data acquisition and sorting was performed using Microsoft Excel 2010. Statistical analysis was performed using IBM SPSS Statistics version 25. Descriptive analysis was performed for BMI, ethnicity, parity, diabetic status and period of amenorrhoea at booking. Quantitative variables were presented as mean and standard deviation; qualitative variables, as absolute numbers (n) and percentage (%).

3. RESULTS AND DISCUSSION

3.1 Results

During the study period, there were 14443 deliveries in Sultanah Aminah Hospital. Data was extracted for a total of 128 patients which comprised of 21 cases of termination of pregnancy, 26 neonatal admissions to NICU due to fetal anomaly and 81 cases of stillbirths. Of these, 31 patients have a non-NTD diagnosis, 10 mothers with no inpatient admission records presumably delivered at another hospital and 70 of the paper-based medical records could not be located. Hence, the total number of NTD-affected

subjects included in the dataset for analysis was 17, as demonstrated in Fig. 1. Table 1 showed the results of maternal characteristics of women with NTD-affected pregnancy and the general obstetric population of 2015.

3.1.1 Incidence of NTDs

The incidence of NTD-affected pregnancy presented to the study setting was 1.2 per 1000 deliveries. There were 17 patients included for analysis, 5 were livebirths NTD, 11 had terminations of pregnancy due to NTD and 1 stillbirth due to NTD.

3.1.2 Types of NTDs

Of the 17 included cases, anencephaly (52.9%) was the most common NTD subtype, followed by hydrocephalus (17.6%), holoprosencephaly (11.8%), spina bifida (11.8%) and myelomeningocele (5.9%). Fig. 2 showed the number of cases for different types of NTDs.

3.1.3 Body Mass Index (BMI)

Upon descriptive analysis, the average BMI of these women was slightly higher than normal

weight with a mean of 25.45 kg/m² and standard deviation of 5.07. The proportions of women with NTD-affected pregnancies were 5.9% for underweight women, 47.1% for normal weight women, 29.4% for overweight women and 17.6% for obesity Class I women. There were no women with NTD-affected pregnancy that have a BMI of equal or more than 35 kg/m². In the general obstetric population, 55.2% of women has a BMI of less than 25 kg/m². 44.8% of women are overweight or obese, with the proportion of 27.1% and 17.7% respectively. Among the obese population, 12.1% of them was of obesity Class I, 4.2% of obesity Class II and 1.4% of obesity Class III.

3.1.4 Maternal characteristics covariates

3.1.4.1 Age

The mean age of women with NTD-affected pregnancies were 30 years with a standard deviation of 4.7 years. Majority of women were in the age group of 26 to 30 years (52.9%), followed by 23.5% in the age group of 31 to 35 years, 11.8% for 21 to 25 years and 11.8% were more than 35 years. Similarly, the majority of women in the general obstetric populations were in the age group of 26 to 30 (35.5%).

3.1.4.2 Ethnicity

Most of the women with NTD-affected pregnancy were Malaysians of Malay ethnicity (58.8%), followed by 23.5% Chinese and 17.6% Indian Malaysian women. The obstetric population of

HSAJB comprises 69.7% women of Malay ethnicity, 12.8% Chinese and 6.9% Indian. 10% of women in the population were of other ethnicities. The highest incidence of NTD-affected pregnancy was seen in Indian women, and the lowest was among Malay women, as shown in Table 2.

3.1.4.3 Parity

Most of the women with NTD-affected pregnancy were multigravida (70.6%), compared to 29.4% of primigravida women.

3.1.4.4 Period of amenorrhea during booking

The average POA at booking for women with NTD-affected pregnancy was during early pregnancy, with a mean of 13.9 weeks and standard deviation of 6.5. There were only two women (11.8%) that had a booking of more than 20 weeks.

3.1.4.5 Diabetic status

Half of the women with NTD-affected pregnancy were non-diabetic. 12.5% of women had pre-existing diabetes (one of the women had type 1 diabetes, and the other had type 2 diabetes). There was one case (6.3%) with GDM. However, five (31.3%) of the cases did not have their diabetic status recorded. In the general obstetric population of HSAJB, a huge proportion of women were non-diabetic (92.4%). GDM constitutes 7.2% of the remaining population, followed by 0.3% with pre-existing diabetes.

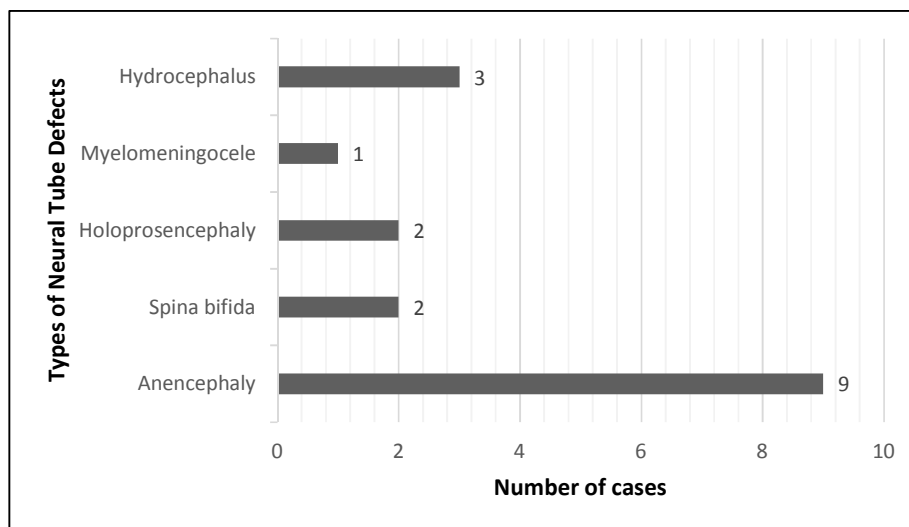


Fig. 2. Number of cases for different types of neural tube defects

Table 1. Maternal characteristics of women with NTD-affected pregnancy and the general obstetric population

	NTD-affected pregnancy, n=17 n(%)	General obstetric population [†] n= 14443 n(%)
BMI categories (kg/m²), mean (SD)	25.45 (5.07)	
Underweight (BMI <18.5)	1 (5.9%)	7977 (55.2%) [‡]
Normal weight (BMI 18.5 – 24.9)	8 (47.1%)	
Overweight (BMI 25 – 29.9)	5 (29.4%)	3911 (27.1%)
Obesity Class I (BMI 30 – 34.9)	3 (17.6%)	1750 (12.1%)
Obesity Class II (BMI 35 – 39.9)	0 (0.0%)	604 (4.2%)
Obesity Class III (BMI ≥40)	0 (0.0%)	199 (1.4%)
Age (years), mean (SD)	30.0 (4.7)	
<21	0 (0.0%)	941 (6.5%)
21-25	2 (11.8%)	3036 (21.0%)
26-30	9 (52.9%)	5134 (35.5%)
31-35	4 (23.5%)	3570 (24.7%)
>35	2 (11.8%)	1762 (12.2%)
Ethnicity		
Malay	10 (58.8%)	10072 (69.7%)
Chinese	4 (23.5%)	1853 (12.8%)
Indian	3 (17.6%)	995 (6.9%)
Others	0 (0.0%)	1451 (10.0%)
Missing	0 (0.0%)	72 (0.5%)
Parity		
Primigravida	5 (29.4%)	-
Multigravida	12 (70.6%)	-
Timing of booking (weeks), mean (SD)	13.9 (6.5)	
≤20 weeks	14 (82.4%)	-
>20 weeks	2 (11.8%)	-
Missing	1 (5.9%)	-
Diabetic status		
Non-diabetes	9 (52.9%)	13350 (92.4%)
Pre-existing	2 (11.8%)	48 (0.3%)
Gestational diabetes mellitus (GDM)	1 (5.9%)	1045 (7.2%)
Missing	5 (29.4%)	0 (0.0%)

[†] National Obstetric Registry did not have the data of parity and timing of booking for the general obstetric population; [‡] Data from National Obstetric Registry has merged the BMI category of both underweight and normal weight

Table 2. Incidence of neural tube defects in different ethnic groups

Ethnicity	Total number of NTD cases	Total number of deliveries	Incidence per 1000 deliveries [†]
Malay	10	10072	0.993
Chinese	4	1853	2.159
Indian	3	995	3.015

[†] Incidence per 1000 deliveries was obtained by dividing the total number of NTD cases with the total number of deliveries of each ethnicity and multiply by 1000

3.2 Discussion

NTD is a relatively uncommon condition in the general population. The findings from our study noted an NTD incidence of 1.2 per 1000 deliveries, which was slightly lower than the

global estimation of the prevalence of NTD-affected deliveries of 1.9 per 1000 deliveries [3]. Furthermore, after exclusion of stillbirth and termination of pregnancy data, our study showed the incidence of livebirth NTD of 0.34 per 1000 livebirth. In comparison to previous literature, the

findings from our study suggest a decreasing trend in the incidence of NTDs in Malaysia. Over the last two decades, the livebirth incidence of NTDs has dropped from 1.29 per 1000 livebirth to 0.42 per 1000 livebirth in the 1980s and 2009 respectively [10,15] the incidence continued to fall to 0.35 per 1000 livebirth based on this study.

One explanation for the low incidence as compared to those reported by previous authors could be the increased acceptance and compliance of periconceptional folic acid supplementation to a bigger patient population. This improvement can be seen via an observation from two studies, with the proportion of Malaysian women with serum folate deficiency has showed a striking reduction from 58.5% in 1982 to 15.1% in 2016 [16,17]. The improved serum folate level amongst Malaysian women could therefore reflected the downward trend of NTDs in Malaysia over the years. Also, spontaneous miscarriages may contribute to severe NTD not making it to term.

3.2.1 Maternal obesity

With the rising prevalence of obesity among women of childbearing age, it was believed that the increasing prevalence of maternal obesity was inevitable. In addition to that, the meta-analysis of 1,758,832 patients has proven maternal obesity as an important risk factor of causing NTDs [6]. Researchers has also discovered a dose response relationship between maternal BMI and risk of NTDs, with the OR of NTDs was 1.040 for every 1 kg/m² BMI increased, 1.214 for every 5 kg/m² BMI increase and 1.475 for every 10 kg/m² BMI increase in mother respectively [6]. Therefore with the robust evidence, this study initially hypothesized that there will be more women who are overweight and obese in the study population, compared to women of normal healthy BMI. Interestingly, there was an equal distribution of women who have normal BMI (47%) compared to women who are overweight and obese (47%). Only nearly one fifth of the cases were obese. Therefore, our initial hypothesis was not supported by the findings of this study. This finding can be explained by Type 2 error which provided a false negative result due to the small sample size of this study. As this study was the first in Malaysia to examine maternal BMI in women with NTD-affected pregnancies, we could not compare our findings with any existing Malaysian literature.

The incidence of obesity in our study was 17.6% for cases and 17.7% for the general obstetric population, these figures mirrors with the national figure for obese adult female in 2016 of 18% [18]. In addition to that, the profound similarity in the pattern of BMI distribution between the cases and general obstetric population in our study could further extrapolate that there was no association between maternal BMI and NTDs. Without data on normal pregnancy, it is not possible to determine whether maternal obesity is associated with the risk of NTDs. Therefore, extensive research is still necessary to statistically examine the risk effect of maternal obesity on NTDs.

3.2.2 Maternal characteristics

This study has also collected data on some other maternal characteristics. Upon examining their characteristics, the majority of cases in this study were found to be in the age group of 26 to 30, Malay ethnicity, multigravida, had their booking visit within 20 weeks of amenorrhea and were non-diabetic. From our findings, none of the other maternal characteristics showed an association with maternal BMI and this could be due to the small sample of cases in our study.

The peak maternal age group amongst the cases and general obstetric population was 26 to 30 years. In the group of women with NTD-affected pregnancies, they were generally young with a mean age of 30.0 years but was older in comparison to the study by Boo et al. [10] which showed a mean maternal age of 28.5 years old. This could be explained by the increase in maternal age at childbirth. In recent decades, the age of women at childbirth in many countries has also increased for approximately 2 to 5 years [19].

Moreover, there was an observed difference in the incidence of NTDs amongst the three different ethnic groups. From our findings, women of Indian ethnicity (3.02 per 1000 deliveries) had the highest incidence of NTDs in the study population, followed by Chinese (2.16 per 1000 deliveries) and Malay (0.99 per 1000 deliveries) ethnicity. The nationwide study by Boo et al. [10] has observed the highest incidence of NTDs among women of Sarawak and Sabah indigenous groups, followed by women of Indian ethnicity at a rate of 0.54 per 1000 livebirths. In a systematic review published in 2015, the birth prevalence of NTDs in India was higher compared to other countries [20]

Similarly, among South-East Asian countries, India has the highest prevalence for NTDs at 66.2 per 10,000 births, where the lowest prevalence for the region was in Thailand, at 1.9 per 10,000 births [21]. There has been little study to date that explored the high incidence of NTDs among Indian ethnicities. One of the possible aetiology could be explained by the role of vegetarian dietary habits. In a case-control study conducted in India, women who consumed a vegetarian diet had an increased risk of having infants with NTDs, compared to those with a non-vegetarian diet [22].

Vegetarian diet usually consists of plant-based food and the exclusion of animal products. Mothers who strongly adhere to a vegetarian dietary habit during pregnancy will develop vitamin B12 deficiency, as this micronutrient is solely found in animal products. A reduced consumption of vitamin B12 especially during early trimester results in low maternal serum concentration of vitamin B12, predisposing the women of having NTDs infants [23]. The observation of high incidence of NTDs in the Malaysian Indian population render further investigation to identify risk factors, such as dietary habits, that may predispose them to NTDs.

In regard to maternal obesity and ethnicity, the Malaysian National Health and Morbidity Survey published in 2015 has shown that Indians have the highest rate of obesity, followed by Malay and Chinese [24]. In our study, women of Indian ethnicity did not have the highest prevalence of maternal obesity, which could be explained by Type 2 error due to the small sample size. However, the high incidence of NTD-affected pregnancy amongst Indian women from our study and highest rate of obesity amongst Malaysian Indian renders further investigation.

Upon examining the parity of the cases in our study, we observed the majority of these women were multigravida, meaning that they have been pregnant for more than once before. There have been studies that suggest a correlation between parity and risk of congenital malformations. In particular, a meta-analysis consisting of 15 studies done by Feng and team [25] were able to prove a statistically significant association between increasing parity and risk of developing congenital heart disease. Although the specific pathogenesis behind this relationship was unclear, some studies suggested nutrition depletion has been more commonly seen in

multiparous women compared to nulliparous women, which would possibly contribute to the rise in risk of NTDs. According to the findings from a retrospective population-based study conducted by Moser and colleagues [26], they found that women who have given birth to more than one child have a lower adherence rate of prenatal recommendations of folic acid supplementation than those who had never delivered. Furthermore, it has been argued that parity could also indirectly cause congenital abnormalities via increasing the risk of maternal obesity. In two population-based study, the researchers noted that maternal obesity and increased weight circumference was more prevalent in multiparous women compared to primiparous women [27,28].

In Malaysia, the advocated timing for booking visits is before the 12 weeks of period of amenorrhea (POA) [29,27]. Our findings demonstrated that the mean POA for the cases in our study to be 13.9 weeks, which was almost two weeks later than the recommended schedule. There were two women with NTD-affected pregnancies that were reported to have their booking visit after 20 weeks of POA. The rather late booking period for the cases in this study could be due to lower awareness on the importance of early antenatal visit and geographical location of primary care centers. Later presentations to professional healthcare providers could also indicate a lack of pre-pregnancy counselling and lack of folic acid supplementation in this group of women, therefore presenting a higher risk of NTDs to their offspring.

In regard to the diabetic status of the cases included in our study, the majority of these women were non-diabetic. This finding is inconsistent with the notion that hyperglycemia during pregnancy is a teratogen to the developing fetus [30]. As both conditions often coexist, the low incidence of maternal obesity had similarly reflected a low incidence of maternal diabetes in this study group.

3.3 Strengths and Limitations

The present study has a few key strengths. The included patients for this study were not limited to livebirth deliveries, but also stillbirth and termination of pregnancy due to NTDs. Unlike the previous NTD-related research in Malaysia, such as the study by Boo et al. [10] and Sahmat et al. [12] which included only livebirth data. The

inclusion of patients from the three domains allow the involvement of a wider obstetric population during patient identification. The collected maternal characteristic was therefore able to more accurately represent women with NTD-affected pregnancy in Malaysia. Maternal BMI was collected using the recorded BMI from the patient medical records. These recorded BMI was obtained using the patient's measured height and weight, which limits recall bias. Furthermore, the study utilized the classification of BMI by WHO, which is an internationally recognized and standardized classification.

There exist a few limitations in the present study. There was an issue of incomplete outcome data in this study. Up to 49% of the patient medical folders could not be located from the record room of the Department of Medical Records of HSAJB, which may result in an underestimation of the actual incidence of NTD-affected pregnancy. As part of the study design, we traced the inpatient data of mothers of neonates admitted to the NICU for NTD-related medical problems. The limitation of this design is that not all mothers of these children were admitted to the hospital involved in this study. This phenomenon can be explained by the fact that these children with NTDs were delivered in smaller district hospitals, who subsequently developed complications requiring NICU treatment. Furthermore, the livebirth data for our study was restricted to patients who have NTDs that require admission into NICU. Patients with NTDs have a wide spectrum of clinical presentation and milder forms of NTDs may not require intensive care [28]. Another limitation of the study is the small sample size. As this study was only conducted in a single-centre, the findings from this study may be insufficient to represent the obstetric population at the state and national level. Lastly, due to the limitation of a retrospective study, we could not obtain the information on folic acid supplementation for these women which was inconsistently documented in the hospital's medical records.

3.4 Significance and Future Direction

Despite the abundance of evidence from other regions of the world, the data from Asia, particularly Malaysia is severely lacking. Therefore, it is important to investigate the relationship of increased maternal BMI and the risk of NTD in the Malaysian setting so that early preventative policies can be implemented to identify at-risk individuals and encourage women

of reproductive years to maintain a healthy BMI. This study is significant as it is one of the earliest studies conducted in Malaysia to investigate maternal obesity in women with NTD-affected pregnancy, which will be useful to guide future research.

In regard to the future direction of this study, we intend to look into a wider population of cases to increase the number of samples for analysis. This unusually high number of NTDs occurred amongst women of Indian ethnicity in our study renders further research to determine whether similar results could be replicated by increasing the sample size of patients. The small number of data presented in our study may not be conclusive enough to represent the scenario in the local setting. This study is still ongoing as the research team continues to collect patient data from year 2016 to 2019. The increased study population will allow us to deepen our understanding on the maternal characteristics, particularly maternal obesity, in women with NTD-affected pregnancy in Malaysia and contribute to the body of data in the local region.

4. CONCLUSION

In conclusion, the findings from this study has demonstrated an incidence of maternal obesity in women with NTD-affected pregnancy as 17.6%. This does not support the initial hypothesis that the majority of women with NTD-affected pregnancy will be overweight or obese. Majority of the women in this study were young, non-diabetic, had a relatively late booking and were multigravidas. We do note a higher incidence of NTDs in the Indian population as compared to the Chinese and Malay ethnicity, which require further investigations.

As this research continues to include a wider sample of women with NTD-affected pregnancy for analysis, the final results of this research will contribute to the limited body of evidence on the maternal characteristics of women who have had pregnancies with NTDs in Malaysia. Despite the low incidence of maternal obesity in our study, women who intend to get pregnant are strongly recommended to maintain a healthy BMI during the pre-pregnancy and periconceptional period, as well as throughout pregnancy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that necessary ethical approval has been obtained from the Malaysian Medical Research Ethics Committee (NMRR ID: NMRR-17-583-34577) and Monash University Human Research Ethics Committee (Project ID: 9581), and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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